Available online at www.sciencedirect.com
ScienceDirect
Environmental Research 106 (2008) 89–95
Environmental Research
www.elsevier.com/locate/envres

Biomarkers of manganese exposure in a population living close to a mine and mineral processing plant in Mexico

Sergio Montes[a], Horacio Riojas-Rodríguez[b], Eva Sabido-Pedraza[b], Camilo Ríos[a,*]

[a]*Departamento de Neuroquímica, Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suárez", Insurgentes Sur 3877, La Fama, Tlalpan, Mexico city, México*
[b]*Centro de Investigación en Salud Poblacional, Instituto Nacional de Salud Pública, México*

Received 4 August 2006; received in revised form 15 August 2007; accepted 17 August 2007
Available online 29 October 2007

Abstract

Manganese (Mn) is considered an essential metal; nevertheless, excessive Mn exposure in humans is known to affect central nervous system. Mn access to its toxic target, the brain, is a complex phenomenon subject to physiological and physiopathological processes; in which, among others, the route of exposure plays an important role. Mn airborne exposure has gained interest both in occupational and environmental studies in order to understand the effects of low-level, long-term exposure. The objective of the present study was to describe the relationship between blood Mn and prolactin as marker of effect exposure, as well as other variables from subjects dwelling in a mining district in central Mexico environmentally exposed to the metal. This study was conducted on 230 volunteers; blood samples were obtained from cubital vein and hemoglobin, prolactin, lead (Pb), and Mn levels were measured. Non-parametrical Spearman's correlation showed statistical associations between blood and Mn levels and prolactin ($\rho = 0.197$), hemoglobin ($\rho = -0.213$), age ($\rho = -0.186$), and blood lead ($\rho = -0.167$). Multiple regression analysis showed that blood Mn levels as an important factor to determine serum prolactin levels ($\beta = 0.111$, $p = 0.029$) in a model corrected by gender and age. Results suggest that assessment of Mn exposure by biomarkers on general population is complex due to the variability and characteristics of the metal; however, specific subpopulations such as iron-deficient individuals are suspected to accumulate Mn in blood and thus they may be susceptible to the neurotoxic effects of Mn.

Keywords: Manganese; Population; Biomarkers; Prolactin; Hemoglobin

1. Introduction

Manganese (Mn) is an abundant metal. It is essential for living organisms because it serves as an active constituent for several enzymes: mitochondrial superoxide dismutase, glutamine synthetase and pyruvate carboxylase, among others (Prohaska, 1987). However, excessive Mn exposure is known to affect central nervous system by causing psychiatric and neurologic symptoms. Prolonged Mn exposure has been associated to a motor extrapyramidal dysfunction which consists of bradykinesia and dystonia, resembling Parkinson's disease (Mena, 1979; Calne et al., 1994).

As an essential metal Mn is subject to physiologic control systems influencing absorption, distribution, and elimination. In fact, liver plays a role as homeostatic regulator of Mn burden in the body. Excess Mn ingested with food is combined with bile and excreted with the feces (Andersen et al., 1999). Mn exposure by pathways different from oral, such as inhalation, avoids first-pass effect and thus it is expected that this has profound effects on the access of this metal to the central nervous system, as shown in experimental studies (Dorman et al., 2006). Recent interest has been put forward to study long-term, low-level inhalation exposure to Mn in the human because methylcyclopentadienyl Mn tricarbonyl is being used as a gasoline octane booster in some countries (Pfeifer et al., 2004).

The assessment of neurotoxic properties of Mn in occupational and environmental studies faces the problem

*Corresponding author. Fax: +52 55 5424 0808.
E-mail address: crios@correo.xoc.uam.mx (C. Ríos).

0013-9351/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.envres.2007.08.008

of evaluating a naturally occurring metal both in environment and in biological samples. Because of this, the assessment of Mn exposure is based on blood Mn levels altogether with other variables. These markers provide information on specific or derived Mn actions on organisms (Smargiassi and Mutti, 1999).

It is known that Mn causes an altered function in the cerebral dopamine (Verity, 1999), a fact that is tightly related to the psychiatric and expyramidal symptoms during Mn intoxication. Dopamine, among other roles in the central nervous system, regulates negatively the secretion of the hormone prolactin in the anterior pituitary gland. Assessment of prolactin levels in occupationally Mn exposed workers shows that circulating levels of the hormone are high when compared to the control group (Mutti et al., 1996). Mn, as a transition metal, has also been implicated in oxidative stress. Experimental work suggest that Mn increases the production of free radicals measured as increased lipid peroxides, reduced glutathione, metallothionein (Erikson et al., 2004), and other specific biomarkers derived form the actions of Mn on biogenic amines such as dopamine (Graham, 1984; Archibald and Tyree, 1987). Other approaches have been challenged taking into consideration the antagonistic relationship between Mn and iron at levels of transport, distribution, and storage (Aschner and Aschner, 1990). For example, an environmental study shows a negative correlation between blood Mn and total iron in plasma from the women who took part in it (Baldwin et al., 1999).

Mn intoxication has been recently studied using magnetic resonance images. The use of magnetic resonance takes advantage of the paramagnetic properties of the metal; Mn shortens the T1-relaxation time and increases the signal intensity in the MRI and this effect was observed in humans (Nelson et al., 1993) and animals (Eriksson et al., 1992). MRI is reliable as indicator of Mn deposition in the brain (Kim, 2004). Disadvantages for such studies are the high cost and the fact that the subject must be transported to the facilities where the equipment is available.

The objective of the present study was to describe the relationship between blood Mn and prolactin as marker of effect exposure, as well as other variables from subjects dwelling in a mining district in central Mexico environmentally exposed to the metal. The participating people are exposed to breathable Mn dust derived not only from activities in surface mines but also from procedures associated to refining the extracted mineral; specifically, in this particular zone, mineral undergoes a process which consists in grinding and heating Mn material in order to semi-purify Mn oxides. This process is suspected to increase airborne Mn and thus the exposure to this metal. Conclusions based on results derived from this work are intended to evaluate the impact of air Mn on individual's health and living conditions in this particular area.

2. Materials and methods

2.1. Participants and sampling

The present study is part of a larger project aimed to evaluate environmental and health effects of extracting and processing Mn mining product. Details concerning sampling design, geographical, population and sociodemographical data, and mining activity on the zone can be found in Rodriguez-Agudelo et al. (2006).

We selected 300 people by means of a random multi-step procedure. At the moment of sampling, they lived in 8 different communities at different distances, ranging between 0.5 and 7.4 km, from the mining and refining plants on an irregular mountainous zone called "Sierra Madre Oriental". All of the participants from the different communities were informed about the objectives of this study and agreed to collaborate. Inclusion criteria were age 20–85-year old, either men or women (selection was made to be representative for the communities both, in age and gender); living for at least 5 years in the community at sampling moment. Houses of participants were selected randomly and then inhabitants were visited to invite participants to this study. The list of participants was compared with the local census to obtain a final list of subjects to match sociodemographic characteristics of population. Exclusion criteria consisted in miners and ex-mine workers. People suffering from diabetes, liver-related or psychiatric diseases were also excluded. All of the participants from the different communities were informed about the objectives of this study and agreed to collaborate.

Blood samples were taken from cubital venous blood in metal-free Vacutainer EDTA tubes to measure blood Mn as well as other biomarkers: prolactin, hemoglobin and lead.

The present study was approved by the bioethics committee of our institution.

2.2. Blood Mn

Mn content in blood was determined by electrothermal graphite furnace atomic absorption spectrophotometry. Blood samples were treated with a matrix modifier (1% ammonium-dihydrogenphosphate in 0.1% Triton X-100 solution). Twenty microliters of the diluted sample were injected into a 3110 Perkin-Elmer atomic absorption spectrophotometer equipped with a HGA-600 graphite furnace, an AS-60 autosampler and a hollow cathode Mn lamp. Calibration curves were prepared by using a commercially available Mn standard solution (Titrisol, Merck, Mexico) diluted into the same matrix modifier. Quantification limit for blood Mn was 0.5 μg/L. Quality control of the analysis of blood Mn was assured by measuring a biological matrix-based reference material (Bovine Liver from the National Institute of Standards and Technology, 1577b, Gaithersburg, MD, USA) along with the blood samples. A 95% confidence interval for mean Mn in the reference material was employed to determine if blood samples were within the limits of acceptance. Samples were measured in duplicate; every measurement consisted of two injections into graphite furnace, in all cases standard deviation was lower than 10%; if otherwise, sample was reanalyzed. The same procedure was done in the case of blood lead. Results were expressed as micograms of Mn per liter of blood (Montes et al., 2002).

2.3. Blood lead

Lead levels in blood were assessed by using the above described atomic absorption instrument operated with a light source specific for lead. Blood samples (200 μl) were diluted in 800 μl of diluted nitric acid (Suprapur, Merck, Mexico); the clear supernatant was assayed in the previously calibrated instrument. Limit of quantification for lead in blood was 1 μg/dL. In this case, quality control was assured by analysis of blood with known quantities of lead from the lead Wisconsin State Laboratory of Hygiene proficiency program. Results were expressed as micrograms of lead per deciliter of blood.

2.4. Prolactin analysis

Serum prolactin was quantified by microparticle enzyme immunoassay by the axsym system (Abbott Laboratories, IL, USA). The calibration, quality control procedures and reagents were obtained from the manufacturer. Limit of quantification for this technique was 0.6 ng/mL. Reference values were considered 1.61–18.77 ng/mL for males and 1.39–24.2 ng/mL for females.

2.5. Hemoglobin

Blood samples were analyzed to determine hemoglobin by routine procedure in our Institute facilities. References values considered were 14–18 μg/dL for males and 12–16 μg/dL for women.

2.6. Statistical analysis

Data were analyzed by using the statistical software SPSS version 12. Exploratory analysis was applied to data in order to check for normality distribution. When necessary, logarithmic transformations to continuous variables were made to obtain symmetric distribution of values and also to assure non-violation of assumptions of parametric analysis. Bivariate analyses were then applied to select variables associations using bivariate Spearman's correlations. For categorical variables, group comparisons were performed by using Mann–Whitney, $p<0.05$ was considered as significant.

For the construction of multivariate models, bivariate analyses in the form of simple linear regression were first carried out to select variables. For those analyses, variables were log transformed and selected when $p<0.05$, in one-tailed tests. Multivariate modeling was done through least squared multiple regression considering log prolactin as dependent variable as this particular variable was interesting for the present study. We also performed multivariate analysis as canonical correlations.

3. Results

From the sample ($n=230$) of people who agreed to participate in the present study, 146 were women (63.5%) and 84 were men (36.5%). Their mean age was 45.13 ($\pm$15.83) and ranged from 20 to 85 years. Their socio-economic status corresponds to very low-income communities, less than 100 USD per month. Mean scholarship was 3.9 $\pm$ 3.0 years and because of the proportion of gender, most of them were housewives (65%), and 30% were agricultural workers.

Table 1 shows data from the biological variables measured: blood Mn, blood lead, serum prolactin and hemoglobin. Blood levels of Mn, Pb and prolactin did not show a normal symmetrical distribution, thus non-parametric tests were applied to analyze data. It was found that the levels of women's blood Mn (median 9.20 μg/L, minimum 3.3 maximum 21.5 μg/L) significantly higher than those from men (median 8.00 μg/L, minimum 3.6, maximum 26.5), $p<0.05$, Mann–Whitney U test.

Bivariate analyses showed several associations, revealed by the Spearman correlation between Mn and the variables measured; results are shown in Table 2. Scatter plots to show those correlations are depicted in Fig. 1.

Multiple regression models were adjusted to data by considering log prolactin as dependent variable; blood Mn as independent variable and hemoglobin, age and blood lead as covariates to produce a saturated model with 0.456 adjusted R^2. After stepwise analysis, the model was reduced to three variables explaining levels of serum prolactin; those were gender, age and blood Mn. The final standardized coefficient for log Mn was 0.111 ($p=0.029$) determining levels of prolactin after gender and age correction and confirming the positive association between blood Mn and prolactin, as shown in Fig. 1A.

Results from canonical correlations between blood Mn and the other variables were as follows: prolactin (partial correlation = 0.188, $P=0.002$); Hemoglobin (partial correlation = −0.159, $P=0.008$); Age (partial correlation = −0.164, $P=0.007$) and blood lead (partial correlation = −0.119, $P=0.037$).

4. Discussion

The study of Mn as an environmental pollutant has gained importance due to the use of methylcyclopentadienyl manganese tricarbonyl (MMT), an organic material, as anti-knock additive for gasoline in countries such as Canada, USA and Australia (Lynam et al., 1999; Gulson et al., 2006). For this reason, some researchers have considered it important to study the low-level exposure to airborne Mn (Mergler et al., 1999). In this context, the population that participated in this study showed relevant characteristics: they are environmentally exposed to

Table 1
Biomarkers measured in 230 people from a community environmentally exposed to manganese

Variable	Mean	Std. dev.	Median	Minimum	Maximum
Blood manganese (μg/L)	9.68	4.13	8.85	5	26.5
Blood lead (μg/dL)	10.46	4.77	9.50	2.0	36.5
Hemoglobin (g/dL)	14.30	1.40	14.20	9.8	18.4
Prolactin (ng/mL)	17.39	6.51	16.80	5.8	45.3

Table 2
Results from Spearman's non-parametric correlations between markers of manganese exposure

		Prolactin	Blood lead	Hemoglobin	Age
Blood Mn	Correlation coefficient (ρ)	0.197	−0.167	−0.213	−0.186
	P	0.003	0.012	0.001	0.012

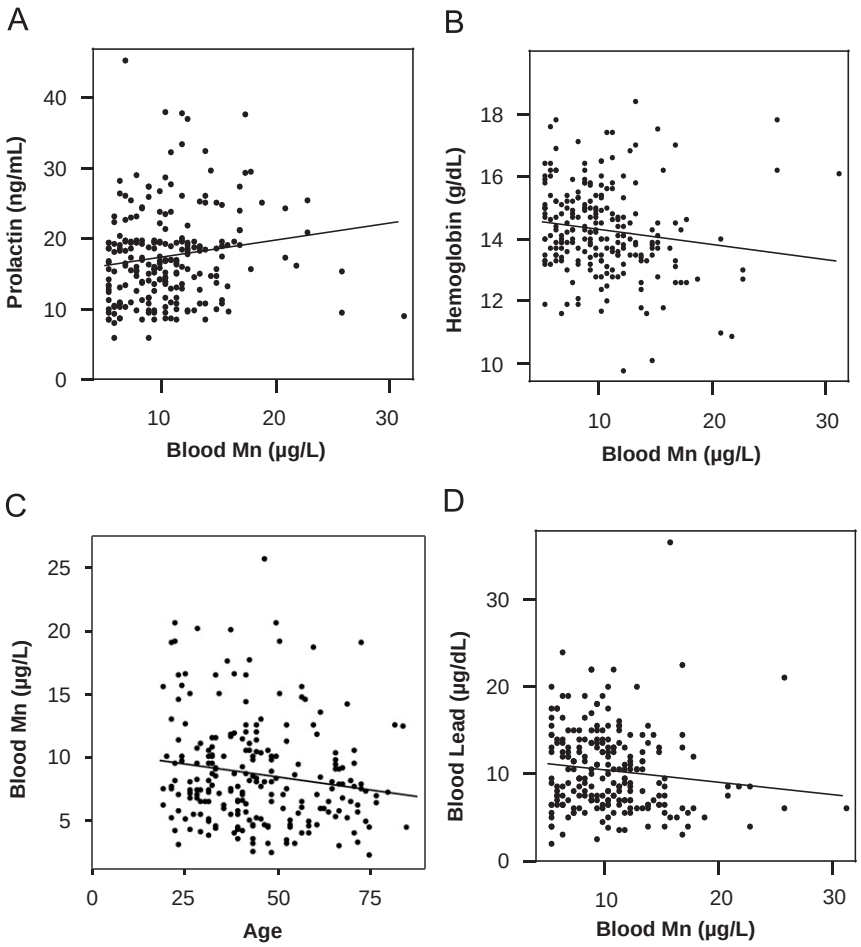

Fig. 1. Scatter plot showing main relationships found between manganese and (A) prolactin, (B) hemoglobin, (C) age and (D) lead.

airborne Mn, they show a chronic exposure for at least 5 years to the metal, and finally, this study was conducted on general population, thus men and women with a wide range of ages and conditions were included. Results are descriptive but with special emphasis on the relationship between the different variables measured.

Data from the present study show that Mn blood levels of participants were higher than those from non-exposed subjects from other studies (from 5.7 to 7.0 µg/L) but lesser than occupationally exposed individuals (from 10.3 to 13.6 µg/L) (Roels et al., 1987; Apostoli et al., 2000). However, blood Mn levels should be taken carefully, due to the fact that circulating blood Mn reflects both, historical Mn exposure and exposure at the moment of sampling whatever the source; that is, breathable airborne or orally ingested (metal present in food). In fact, some authors consider that levels of Mn in blood poorly reflects the body burden of the metal in chronic exposure (Lu et al., 2005; Apostoli et al., 2000). This assumption is based on experimental studies showing that $t_{1/2}$ of Mn in blood is about 2 h (Zheng et al., 2000). Thus, blood Mn provides little information regarding target organs for Mn toxicity, for example the brain, where $t_{1/2}$ is about 50 days (Newland et al., 1987). The differences in these velocities suggest a lack of concordance between blood Mn and actual levels in tissues, especially in brain. However, in the present study, blood Mn is taken as an indirect reference to be associated to some other variables that could be affected by Mn exposure, the markers of effects.

The rationale to include serum prolactin assessment was based on the fact that Mn exposure causes dopamine disturbances in brain (Bird et al., 1984), and dopamine serves as an inhibitor to the release of prolactin from the endocrine portion of pituitary gland. In fact, serum prolactin has been found increased in workers exposed to Mn (Mutti et al., 1996) and it has been used as a biomarker in non-occupational studies in which its serum levels correlate positively to blood Mn (Takser et al., 2004). Here, it was found that blood Mn positively correlated to serum prolactin as shown in Table 2. Although this relationship showed a low Spearman's correlation coefficient ($\rho = 0.197$), it reached statistical significance. It was further confirmed by the results of multiple regression analysis, in which it was observed that the main predictors of serum prolactin were gender, age and blood Mn levels. Such a finding suggests some central nervous system influence of Mn, though actual Mn actions on physiopathological consequences were not assessed.

Age correlated negatively with blood Mn. This finding confirms similar results from other studies (Baldwin et al., 1999) that have shown tendencies for blood Mn to decrease with age. The meaning of such a relationship remains an interesting matter for future studies because we cannot exclude the possibility of physiologic compensatory mechanisms for the absorption or elimination of Mn.

Experiments carried out in rodents have shown that iron-deficiency is a risk factor to accumulate Mn in brain. In other words, animals with iron-deficient anemia accumulate more Mn in brain and thus they were more susceptible to Mn exposure (Erikson et al., 2002). Results derived from the present environmental work revealed that the relationship between Mn and iron may be also present in exposed humans because a statistical significant negative correlation between blood Mn and hemoglobin was observed (Table 2). This particular finding is in agreement with a recent report in which levels of Mn in blood were higher in patients with iron deficient anemia in comparison to controls. Furthermore, iron therapy increased hemoglobin levels and diminished blood Mn in the same patients (Kim et al., 2005), which suggests an inverse relationship between both metals. Such a relationship has been explained from the fact that both metals share similar systemic absorption and blood transport and even more, similar brain transport mechanisms (Finley, 1999; Aschner et al., 1999). Studies with human subjects have shown that Mn toxicokinetics are different in men in comparison to women, specifically it has been observed that women absorb more Mn than men. This phenomenon, in turn, has been related to iron status and to other iron related proteins such as ferritin, which is found higher in men than in women (Finley et al., 1994; Finley, 1999). Thus, the differences in Mn blood levels observed herein in men in comparison with women could be related not only to hemoglobin, but also to other iron-related proteins such as ferritin, a fact that reinforces the global idea of iron–Mn antagonism. Mn–Hemoglobin correlation may have other implications: the communities studied here show important social margination, thus malnutrition is a common problem, and it could be a factor to be considered regarding Mn exposure.

Our group had previously demonstrated that the use of handcraft lead-glaze ceramics in cooking activities and also used for food storage release important quantities of Pb to food, that eventually are consumed and absorbed by oral route in rural communities in central Mexico (Rojas-Lopez et al., 1994). The inhabitants of the area studied are also exposed to Pb through the same mechanism; thus it is a concern of the present work to asses the participation of Pb as a possible confounder for the final outcomes of Mn exposure, for this reason we planned to measure prospectively Pb along with Mn. In the present study, both metals were determined in whole blood, showing a negative correlation. In this regard, it has been observed that Pb in whole blood resides predominantly erythrocytes (Leggett, 1993); in the case of Mn approximately 66% is also present in these cells (Alarcon et al., 1996). The negative relationship for both metals observed here may be the result from a long-term competition for residence in the red blood cells. A second possibility involves the calcium homeostasis, because it has been observed that Mn is able to inhibit the $Ca^{2+}Mg^{2+}$ ATPase, a pump located in the membrane of erythrocytes (Yazbeck et al., 2006), in addition to its capacity to alter calcium in the mitochondria (Gavin et al., 1999). Calcium ingestion is also known to affect lead negatively (Mahaffey, 1990), thus we may find calcium homeostasis as a common target for both metals. However, this relationship could be much more complex and deserves specific studies.

With regard to the associations found between variables, it is interesting that multiple correlation analysis, in the form of canonical correlations, applied to data produced similar significant associations in the bivariate analysis, suggesting that biomarkers are all independently correlated to blood Mn.

Results from this population based study are important because they could be taken as a reference to further investigate biomarkers related to the final outcomes of Mn action on brain functions, specially studies dealing with a broad spectrum of conditions of participants (age for example) in which one may find specific groups of susceptibility, for example the elderly and children in which we may not expect the same effects. In the former, we may explore postural and/or motor disturbances as has been done in occupationally exposed subjects (Mergler et al., 1994). On the later, it would be interesting to explore not only motor, but also cognitive tests (Bouchard et al., 2007). In fact, we have started as part of a larger project, to explore final outcomes of environmental Mn exposure in this area by looking for motor disturbances in the people living there (Rodriguez-Agudelo et al., 2006), in whom alterations in the ability to perform tasks that evaluate coordination was observed. Our final consideration is that Mn environmental exposure is a challenging problem, and a single biomarker is not enough to draw conclusions about it, especially in community-based studies in which a great range of variability and conditions of individuals can be found. However, more studies are needed to explore easy to access and reliable biological variables that may help to better characterize and understand the influence of Mn to health in environmentally exposed communities.

Information on funding and ethics

This work was financially founded by the International Development and Research Center, Canada. Project number 100662 with further contributions of the Health Services of Hidalgo and the State Council of Ecology, Hidalgo and CONACyT Grant no. 51541.

This work was approved by the ethics committee of the National Institute of Neurology and Neurosurgery, Mexico.

All of the participants received written information concerning the type of the study and signed an agreement.

At the end of the analyses, subjects received their personal results and an explanatory talk about environmental manganese.

References

Alarcon, O.M., Reinosa-Fuller, J.A., Silva, T., Ramirez, M., Gamboa, J., 1996. Manganese levels in serum of healthy Venezuelan infants living in Merida. J. Trace Elem. Med. Biol. 10, 210–213.

Andersen, M.E., Gearhart, J.M., Clewel, H.J., 1999. Pharmacokinetic data needs to support risk assessments for inhaled and ingested manganese. Neurotoxicology 20, 161–172.

Apostoli, P., Lucchini, R., Alessio, L., 2000. Are current biomarkers suitable for the assessment of manganese exposure in individual workers? Am. J. Ind. Med. 37, 283–290.

Archibald, F.S., Tyree, C., 1987. Manganese poisoning and the attack of trivalent manganese upon catecholamines. Arch. Biochem. Biophys. 256, 638–650.

Aschner, M., Aschner, J.L., 1990. Manganese transport across the blood–brain barrier: relationship to iron homeostasis. Brain Res. Bull. 24, 857–860.

Aschner, M., Vrana, K.E., Zheng, W., 1999. Manganese uptake and distribution in the central nervous system. Neurotoxicology 20, 173–180.

Baldwin, M., Mergler, D., Larribe, F., Belanger, S., Tardif, R., Bilodeau, L., Hudnell, K., 1999. Bioindicator and exposure data for a population based study of manganese. Neurotoxicology 20, 343–353.

Bird, E.D., Anton, A.H., Bullock, B., 1984. The effect of manganese inhalation on basal ganglia dopamine concentrations in Rhesus monkey. Neurotoxicology 5, 59–66.

Bouchard, M., Laforest, F., Vandelac, L., Bellinger, D., Mergler, D., 2007. Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. Environ. Health Perspect. 115, 122–127.

Calne, D.B., Chu, N.S., Huang, C.C., Lu, C.S., Olanow, W., 1994. Manganism and idiopatic Parkinson's disease: similarities and difference. Neurology 44, 1583–1586.

Dorman, D.C., Struve, M.F., Marshall, M.W., Parkinson, C.U., James, R.A., Wong, B.A., 2006. Tissue manganese concentrations in young male rhesus monkeys following subchronic manganese sulfate inhalation. Toxicol. Sci. 92, 201–210.

Erikson, K.M., Shihabi, Z.K., Aschner, J.L., Aschner, M., 2002. Manganese accumulates in iron-deficient rat brain regions in a heterogeneous fashion and is associated with neurochemical alterations. Biol. Trace Elem. Res. 87, 143–156.

Erikson, K.M., Dobson, A.W., Dorman, D.C., Aschner, M.A., 2004. Manganese exposure and induced oxidative stress in the rat brain. Sci. Total Environ. 334–335, 409–416.

Eriksson, H., Tedroff, J., Thomas, K.A., Aquilonius, S.M., Hartvig, P., Fasth, K.J., Bjurling, P., Langstrom, B., Hedstrom, K.-G., Heilbronn, E., 1992. Manganese induced brain lesions in *Macaca facsicularis* as revealed by positron emission tomography and magnetic resonance imaging. Arch. Toxicol. 66, 403–407.

Finley, J.W., 1999. Manganese absorption and retention by young women is associated with serum ferritin concentration. Am. J. Clin. Nutr. 70, 37–43.

Finley, J.W., Johnson, P.E., Johnson, L.K., 1994. Sex affects manganese absorption and retention by humans from a diet adequate in manganese. Am. J. Clin. Nutr. 60, 949–955.

Gavin, C.E., Gunter, K.K., Gunter, T.E., 1999. Manganese and calcium transport in mitochondria: implications for manganese toxicity. Neurotoxicology 20, 445–453.

Graham, D.G., 1984. Cathecholamine toxicity a proposal for the molecular pathogenesis of manganese neurotoxicity and Parkinson's disease. Neurotoxicology 5, 83–95.

Gulson, B., Mizon, K., Taylor, A., Korsch, M., Stauber, J., Davis, J.M., Louie, H., Wu, M., Swan, H., 2006. Changes in manganese and lead in the environment and young children associated with the introduction of methylcyclopentadienyl manganese tricarbonyl in gasoline—preliminary results. Environ. Res. 100, 100–114.

Kim, Y., 2004. High signal intensities on T1-weighted MRI as a biomarker of exposure to manganese. Ind. Health 42, 111–115.

Kim, Y., Park, J.K., Choi, Y., Yoo, C.I., Lee, C.R., Lee, H., Lee, J.H., Kim, S.R., Jeong, T.H., Yoon, C.S., Park, J.H., 2005. Blood manganese concentration is elevated in iron deficiency anemia patients, whereas globus pallidus signal intensity is minimally affected. Neurotoxicology 26, 107–111.

Leggett, R.W., 1993. An age specific kinetic model of lead metabolism in humans. Environ. Health Perspect. 101, 598–616.

Lu, L., Zhang, L., Li, J., Gua, W., Liang, W., Zheng, W., 2005. Alteration of serum concentrations of manganese, iron ferritin and transferring receptor following exposure to welding fumes among career welders. Neurotoxicology 26, 257–265.

Lynam, D.R., Roos, J.W., Pfeiffer, G.D., Fort, B.F., Pullin, T.G., 1999. Environmental effects and exposures to Mn from use of methylcyclopentadienyl manganese tricarbonyl (MMT) in gasoline. Neurotoxicology 20, 145–150.

Mahaffey, K.R., 1990. Environmental lead toxicity: nutrition as a component of intervention. Environ. Health Perspect. 89, 75–78.

Mena, I., 1979. Manganese poisoning. In: Vinken, P.J., Bruyn, G.W. (Eds.), Handbook of Clinical Neurology, vol. 36. North-Holland, Amsterdam, pp. 217–227.

Mergler, D., Huel, G., Bowler, R., Iregren, A., Belanger, S., Baldwin, M., Tardif, R., Smargiassi, A., Martin, L., 1994. Nervous system dysfunction among workers with long-term exposure to manganese. Environ. Res. 64, 51–80.

Mergler, D., Baldwin, M., Belanger, S., Larriber, F., Beuter, A., Bowler, R., Panisset, M., Edwards, R., de Geoffroy, A., Sassine, M.P., Hudnell, K., 1999. Manganese neurotoxicity, a continuum of dysfunction: results from a community-based study. Neurotoxicology 20, 327–342.

Montes, S., Alcaraz-Zubeldia, M., Rios, C., Muriel, P., 2002. A method to induce manganese accumulation in the brain of the cirrhotic rat and its evaluation. Brain Res. Protoc. 9, 9–15.

Mutti, A., Bergamaschi, E., Alinovi, R., Lucchini, R., Vettori, M.V., Franchini, I., 1996. Serum prolactin in subjects occupationally exposed to manganese. Ann. Clin. Lab. Sci. 26, 10–17.

Nelson, K., Golnick, J., Korn, T., Angle, C., 1993. Manganese encephalopathy: utility of early magnetic resonance imaging. Br. J. Ind. Med. 50, 510–513.

Newland, M.C., Cox, C., Hamada, R., Oberdorster, G., Weiss, B., 1987. The clearance of manganese chloride in the primates. Fundam. Appl. Toxicol. 9, 134–328.

Pfeifer, G.D., Roper, J.M., Dorman, D., Lynam, D.R., 2004. Health and environmental testing of manganese exhaust products from use of methylcyclopentadienyl manganese tricarbonyl in gasoline. Sci. Total Environ. 334–335, 397–408.

Prohaska, J.R., 1987. Function of trace elements in brain metabolism. Physiol. Rev. 67, 858–901.

Rodriguez-Agudelo, Y., Riojas-Rodriguez, H., Rios, C., Rosas, I., Sabido Pedraza, E., Miranda, J., Siebe, C., Texcalac, J.L., Santos-Burgoa, C., 2006. Motor alterations associated with exposure to manganese in the environment in Mexico. Sci. Total Environ. 368, 542–556.

Roels, H., Lauwerys, R., Buchet, J.P., Genet, P., Sarhan, M.J., Hanotiau, I., de Fays, M., Bernard, A., Stanescu, D., 1987. Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices. Am. J. Ind. Med. 11, 307–327.

Rojas-Lopez, M., Santos-Burgoa, C., Rios, C., Hernandez-Avila, M., Romieu, I., 1994. Use of lead-glazed ceramics is the main factor associated to high lead in blood levels in two Mexican rural communities. J. Toxicol. Environ. Health 42, 45–52.

Smargiassi, A., Mutti, A., 1999. Peripheral manganese biomarkers and exposure to manganese. Neurotoxicology 20, 401–406.

Takser, L., Mergler, D., de Grosbois, S., Smargiassi, A., Lafond, J., 2004. Blood manganese content at birth and cord serum prolactin levels. Neurotoxicol. Teratol. 26, 811–815.

Verity, M.A., 1999. Manganese neurotoxicity: a mechanistic hypothesis. Neurotoxicology 20, 489–498.

Yazbeck, C., Moreau, T., Sahuquillo, J., Takser, L., Huel, G., 2006. Effect of maternal manganese blood levels on erythrocyte calcium pump activity in newborns. Sci. Tot. Environ. 354, 28–34.

Zheng, W., Kim, H., Zhao, Q., 2000. Comparative toxicokinetics of manganese chloride and methylcyclopentadienyl Mn tricarbonyl in Sprague–Dawley rats. Toxicol. Sci. 54, 294–301.